Date of approval: September 4, 2002

FREEDOM OF INFORMATION SUMMARY

Micotil® 300 Injection
(tilmicosin phosphate)

Supplement to NADA 140-929

"…for the treatment of ovine respiratory disease (ORD) associated with *Mannheimia (Pasteurella) haemolytica*."

SUBMITTED BY:

ELANCO ANIMAL HEALTH

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1. GENERAL INFORMATION:

a. NADA Number:	140-929
b. Sponsor:	Elanco Animal Health A Division of Eli Lilly & Co., Lilly Corporate Center, Indianapolis, IN 46285 Drug Labeler Code: 000986
c. Established Name:	Tilmicosin phosphate
d. Proprietary Name:	Micotil® 300 Injection
e. Dosage Form:	Ready-to-use injectable solution
f. How Supplied:	50 mL, 100 mL, and 250 mL multidose amber glass bottles
g. How Dispensed:	R_x
h. Amount of Active Ingredient:	300 mg tilmicosin as tilmicosin phosphate per mL
i. Route of Administration:	subcutaneous injection
j. Species/Class:	Ovine/sheep
k. Recommended Dosage:	a single subcutaneous injection of 10 mg/kg body weight (1 mL/30 kg or 1.5 mL /100 lb body weight)
l. Pharmacological Category:	antimicrobial
m. Indications:	Micotil® 300 Injection is indicated for the treatment of ovine respiratory disease (ORD) associated with *Mannheimia (Pasteurella) haemolytica*.
n. Effect of Supplement:	Provides for the use of tilmicosin phosphate (Micotil® 300) in a new animal species, sheep.

2. EFFECTIVENESS:

Section 514.1(d) of Title 21 of the Code of Federal Regulations (CFR) permits extrapolation of data from a major species to a minor species to satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act with respect to the effectiveness of a new animal drug. A combination of data from sheep (a minor species) and a closely-related approved major species (cattle) were used to support the determination of effectiveness, consistent with the Guideline for Industry – FDA Approval of New Animal Drugs for Minor Uses and minor Species (Guideline #61 FDA/CVM April 1999).

For the purposes of this supplement for use in sheep, a determination of medical equivalence was based on a pharmacokinetic comparison demonstrating that serum concentrations of tilmicosin in sheep and cattle are comparable when tilmicosin is administered as a single subcutaneous injection at a rate of 10 mg/kg. The data for the effectiveness study was generated under INAD 9693 and submitted in a Public Master File (PMF) 5673. A notice of availability of this PMF is published in the Federal Register (65 FR 47992, August 4, 2000).

3. TARGET ANIMAL SAFETY:

The comparative study of tilmicosin pharmacokinetics, conducted under INAD 9693 and published under PMF 5673, in sheep and cattle indicates that the target animal safety of tilmicosin should be comparable in sheep and cattle when administered as a single subcutaneous injection at 10 mg/kg. None of the animals died during the study and no adverse effects of tilmicosin were observed on blood pressure, heart rate, or respiration rate of sheep. The results indicate that tilmicosin can be used safely in sheep at the recommended dose for sheep with a minimum body weight of 15 kg. The availability of this data in PMF 5673 is published in the Federal Register (65 FR 47992, August 4, 2000.

4. HUMAN SAFETY:

a. Toxicology

See the Freedom of Information (FOI) Summary for the approval of the original application for MICOTIL® 300 (NADA 140-929), approved March 24, 1992. A copy of this FOI summary can be obtained from Mrs. Marylin H. Broderick, HFV-12, Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

b. Safe Concentration of Total Residues:

1) Acceptable Daily Intake (ADI): The ADI previously established for tilmicosin is 1.5 mg/person/day or (25 μg/kg body weight/day for a 60 kg person). Ref. 21 CFR 556.735.

2) Safe Tissue Concentrations (STC):

The STC is calculated by dividing the ADI per person by the tissue consumption factors (300 g/day for muscle, 50 g/day for kidney or fat, and 100 g/day for liver.

$STC_{(muscle)}$ = 1.5 mg/day ÷ 300 g/day = 5 μg/g = 5 ppm
$STC_{(kidney\ or\ fat)}$ = 1.5 mg/day ÷ 50 g/day = 30 μg/g = 30 ppm
$STC_{(liver)}$ = 1.5 mg/day ÷ 100 g/day = 15 μg/g = 15 ppm

c. Total Residue and Metabolism Studies

Total residues of ^{14}C-tilmicosin in sheep tissues were evaluated in two studies:

1) Study HRC/LLY36/930447

The Metabolism and Residues of ^{14}C Tilmicosin Following Subcutaneous Administration to Sheep. L.F. Elsom, D.R. Hawkins, D.H. Dighton, A. Kaur, D.M. Cameron, 1993.

Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, U.K.

The purpose of this study was to evaluate the excretion profile of ^{14}C tilmicosin; to assess the depletion of total radioactive residues in edible tissues; to establish the metabolic profiles in edible tissues and compare them with the metabolic profile in urine and to identify and quantify the major metabolites of tilmicosin in sheep.

Fourteen, 10 to 11 week old Beulah-cross lambs, 16 to 23 kg body weight were administered a single subcutaneous injection of ^{14}C tilmicosin at 20 mg/kg body weight. Plasma samples were collected at 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours after dosing. Urine and feces were collected at pre-dose and in 24-hour intervals for up to 7 days from time of dosing. Tissue samples of liver, kidney, lung, skeletal muscle, fat and injection site were collected for radioactivity assay and TLC and HPLC analyses.

A mean total of 85.2% of the radioactivity dosed was excreted in the 7 days after dosing. The majority of the radioactivity was excreted in the feces (a mean of 71.9%). The urine contained a mean of 13.2% of the total dose in the 7 days. Mean concentrations of radioactivity in tissues of treated sheep are summarized in Table 4.1.

Parent tilmicosin accounted for approximately 75% of the urinary radioactivity with metabolites T-1 and T-2 accounting for <1% of the dose. In the liver and kidney, parent tilmicosin and metabolite T-2 were the major components. The concentration of parent tilmicosin in the liver declined while T-2 correspondingly increased as withdrawal time increased.

Table 4.1: Concentrations (ppm) (Mean ± SD) of radioactivity in tissues of sheep following a single subcutaneous dose of ^{14}C-tilmicosin at a dose of 20 mg/kg body weight

Tissue	Sacrifice (days)			
	3	**7**	**21**	**28**
Liver	9.98±0.78	5.77±0.30	3.67±0.72	2.70±0.60
Kidneys	21.09±4.49	4.07±1.35	1.42±0.89	0.55±0.13
Omental Fat	<1.36	<1.32	<1.32	<1.35
Renal Fat	<1.24	<1.15	<1.17	<1.20
Muscle	1.26±0.18	0.57	<0.26	<0.26
Lungs	5.11±0.08	1.53±0.07	NS*	NS
Inj. Site Skin	63.02±25.80	18.74±5.50	32.91±28.83	6.51±5.69
Inj. Site Muscle	43.19±0.33	14.38±2.11	5.32±6.00	1.32±0.51

*Not sampled

2) Study CVLS4/92

Tilmicosin: Metabolism and Residues of ^{14}C Tilmicosin Following Subcutaneous Administration to Sheep. R. M. Parker and A.M. Walker, 1993.

Central Veterinary Laboratory, Weybridge, Addlestone, KT15 3NB, U.K.

The depletion and quantification of ^{14}C tilmicosin in plasma and tissues was studied in 16 sheep after subcutaneous administration of 20 mg/kg body weight tilmicosin. Plasma was collected at 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours after dosing. Kidney, liver, fat, muscle, injection site and lung tissues were collected at days 3, 7, 21 and 28 post-injection. The plasma and tissue samples were assayed by validated HPLC methods.

Values for the mean plasma concentration of tilmicosin ranged from 958.8 ng/mL (T_{max}) at 4 hours post-injection to below the validated limit of determination (50 ng/mL or 0.05 ppm) at 48 hours post-injection. Between 6 and 24 hours, $t_{½}$ was approximately 7 hours and between 48 and 96 hours, $t_{½}$ was approximately 41 hours.

Concentrations of tilmicosin were highest in the injection site and kidney at Day 3 post-injection. At Day 28, mean tilmicosin concentration was 160.0 ng/g (0.16 μg/g) in the liver, 122 ng/g (0.12 μg/g) in the injection site and 63 ng/g (0.63 μg/g) in the kidney. Tilmicosin was not detected in muscle and fat 21 and 28 days after dosing above the limit of detection of the method (50 ppb). Mean concentrations (ppb) of tilmicosin in the tissues of treated sheep are summarized in Table 4.2.

Table 4.2: Concentrations (mean ± SD) of tilmicosin in sheep tissues

Tissue	Days After Dosing			
	3	7	21	28
Liver	2444.0±278.6*	733.0±43.8	310.0±162.7	160.0±116.2
Kidney	12414.0±5226.5	1286.0±500.6	467.3±352.9	73.0±29.9
Muscle	478.5±186.0	193.5±202.9	ND†	ND
Renal Fat	73.0±14.1	ND	ND	ND
Injection Site	20352±3369.7	7067.3±1019.1	3626.5±3544.6	121.8±28.4
Lung	2810.3±871.0	322.5±111.0	NS††	NS

*Values are reported as ppb
†Not determined
††Not sampled

Sheep injected subcutaneously with ^{14}C tilmicosin at 20 mg/kg body weight excrete 85% of the dose within the first 7 days. Plasma concentrations of tilmicosin decline close to the limits of detection by 36 hours. Tissue concentrations of tilmicosin in all tissues are less than the safe concentration for total residues at all sampling times studied and well below the safe concentrations 28 days after dosing.

Because parent tilmicosin accounts for a substantial portion of the dose in urine and of the residue in kidney and liver, it is selected as the marker residue. As in cattle, liver is selected as the target tissue.

Although a separate comparative metabolism report was not provided, a review of work previously conducted to support NADA 140-929 along with the metabolism data provided for sheep demonstrate that the metabolic profiles for sheep and the toxicological species, the rat, are comparable. Therefore, the toxicological species has been autoexposed to the metabolites of tilmicosin present in the edible tissues of treated sheep.

d. Tolerance for the Marker Residue

The total residue and metabolism study in sheep demonstrates that the marker residue, parent tilmicosin, represents approximately 20% of the total residue in liver. When this percentage is applied to the calculated safe concentrations, a tolerance of 3 ppm is calculated for residues of tilmicosin in liver. Applying the 20% to the muscle safe concentration results in a calculated muscle tolerance of 1 ppm. However, consistent with the requested withdrawal period, we are assigning tolerances of 1.2 ppm for sheep liver and 0.1 ppm for sheep muscle. A liver tolerance of 1.2 ppm is the same tolerance value currently assigned to cattle. A muscle tolerance of 0.1 ppm for residues of parent tilmicosin in sheep muscle is the same as the muscle tolerance assigned to cattle and consistent with the Maximum Residue Limit recommended by the 47th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), Rome 1996. Additionally, the analytical method has an LOQ of half the proposed muscle tolerance and can serve as a monitoring method for residues of tilmicosin in sheep tissues. We propose to assign a withdrawal period of 28 days for the use of tilmicosin, as Micotil® 300, in sheep as a single subcutaneous injection at a dose of up to 10 mg/kg body weight.

e. Withdrawal Period

Depletion of residues in the edible tissue of sheep was evaluated in two studies:

1) Study CVLS6/91

Tilmicosin: Residues in Sheep. R.K.P. Patel, R.M. Parker and H.A. Simmons, 1992.

Analytical Chemistry Unit, Central Veterinary Laboratory, New Haw, Weybridge, Surrey KT15 3NB.

The purpose of this study was to measure residues of tilmicosin in sheep after subcutaneous administration to establish an approximate withdrawal period for the parent drug.

Twenty-four 6 month old sheep, Scottish Blackface, 30 to 40 kg body weight were administered single subcutaneous doses of 30 mg tilmicosin/kg body weight into the left dorsolateral chest wall. Liver, kidney, muscle, fat and injection site tissues were collected at Days 14, 21, 28, 35, 42 and 56 post-injection and analyzed by a validated HPLC method with a limit of determination of 50 ng/g (50 ppb).

The highest mean concentration of tilmicosin was in liver at Day 14 (1554 ng/g) and the minimum concentration of tilmicosin was obtained in muscle and fat (all values were below the limit of determination). At Day 28, the mean concentration of tilmicosin in liver was 418.0 ng/g, at injection site, 150.3 ng/g, and in kidney, 82.0 ng/g. At Day 28, residues in muscle and fat residues fell below the limit of determination (50 ppb). Mean concentrations (ppb) of tilmicosin in sheep tissues are summarized in Table 4.3.

Table 4.3: Concentration (ppb) of tilmicosin residues in sheep tissues following subcutaneous administration of Micotil® 300 at a dose of 30 mg/kg body weight

Tissue	Withdrawal (days)					
	14	**21**	**28**	**35**	**42**	**56**
Liver	1554±160	1170±213	418±208	310±126	199±106	81±19
Kidney	478±178	148±65	93±6	68±4	51	<LOQ
Muscle	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Fat	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Injection Site	506±310	641±469	150±95	159±103	161±84	81±29

LOQ=50 ppb

Tilmicosin was metabolized and/or excreted to a great extent during the study interval. Because the dose was three fold higher than the proposed therapeutic dose, residues would be expected to be lower in animals treated with the proposed dose, 10 mg/kg.

2) Study CVLS/23/95

Tilmicosin: Residues in Sheep after its subcutaneous administration. R.K.P. Patel and R.M. Parker, 1995.

Analytical Chemistry Unit, Central Veterinary Laboratory, New Haw, Addlestone, Surrey KT15 3NB.

The purpose of this study was to determine the residues of tilmicosin in tissues at various withdrawal time points after its subcutaneous administration to sheep at the intended use level.

Twenty-eight Swaledale sheep in the weight range 26.2 to 51.2 kg body weight were divided into seven groups of four sheep per group, consisting of 2 males and 2 females. Six of the seven groups were administered single subcutaneous doses of 10 mg tilmicosin/kg body weight into the left dorsolateral chest wall. The seventh group was designated as control and received no injection. Each group was designated for slaughter at one of the following times post-treatment: 14, 21, 28, 35, 42, or 49 days. (The four sheep in the control group were designated for slaughter at 14 days.)

Liver, kidney, thigh muscle, renal fat and injection site tissues were collected at slaughter and analyzed by a validated HPLC method. Mean concentrations (ppb) of tilmicosin in sheep tissues are summarized in Table 4.4.

Table 4.4: Concentration (ppb) of tilmicosin residues in sheep tissues following subcutaneous administration of Micotil® 300 at a dose of 10 mg/kg body weight

Tissue	Withdrawal (days)					
	14	**21**	**28**	**35**	**42**	**49**
Liver	107±11	80±43	<LOQ	59	<LOQ	<LOQ
Kidney	162±76	73±16	<LOQ	<LOQ	<LOQ	<LOQ
Muscle	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Fat	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Injection Site	1527±504	143±55	80±30	<LOQ	<LOQ	<LOQ

LOQ=50 ppb

The highest mean concentration of tilmicosin was in injection site tissue at Day 14 (1527 ng/g for the average of the four sheep) and the minimum concentration of tilmicosin was obtained in muscle and fat (all values were below the LOQ for the method).

The mean residue concentration in the liver tissue was 107 ng/g at Day 14. Residues in liver were less than the LOQ by Day 49.

Summary of the two residue studies is presented in Table 4.5.

Table 4.5. Summary of residues detected at Day 28 post-injection for the two studies

Study no.	**Dose**	**Liver**	Kidney	**Muscle**	Fat	Injection Site
HRC/LLY36/ 930447	^{14}C 20 mg/kg	2.70±0.60	0.55±0.13	<0.26*	<1.20*	1.32±0.51
CVLS4/92	^{14}C 20 mg/kg	0.16±0.12	0.07±0.03	ND†	ND	0.12±0.03
CVLS6/91	cold 30 mg/kg	0.42±0.21	0.09±0.01	ND	ND	0.16±0.1
CVLS/23/95	cold 10 mg/kg	<LOQ	<LOQ	ND	ND	.080±0.03

*Below limits of detection
†not detected
Limit of quantitation (LOQ) = 0.05 µg/g

These studies confirm that residues of tilmicosin resulting from a single subcutaneous injection of Micotil® 300 to sheep at a dose of 10 mg/kg body weight are below the assigned liver and muscle tolerance levels 28 days after treatment, the assigned withdrawal period.

f. Analytical Methods for Residues

The regulatory analytical method for residues is a reverse phase HPLC method with UV detection. The method is available from Residue Chemistry Team (HFV-151), Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

g. User Safety Concerns

User safety concerns associated with direct contact have been satisfactorily addressed by establishing label warnings. In addition, a toll-free number is provided on the label for additional information and reporting adverse events.

5. AGENCY CONCLUSIONS:

The data submitted in support of this supplemental NADA satisfy the requirements of Section 512 of the Food, Drug, and Cosmetic Act and 21 CFR 514.1 of the implementing regulations. The data demonstrate that Micotil® 300 Injection (tilmicosin phosphate), when used under labeled conditions of use is safe and effective for the treatment of ovine respiratory disease (ORD) associated with *Mannheimia* (*Pasteurella) haemolytica*.

The human food safety data demonstrate that residues resulting from a single subcutaneous injection of tilmicosin to sheep at a dose of 10 mg/kg body weight are below the assigned liver and muscle tolerance levels 28 days after treatment, the assigned withdrawal period.

The product remains a prescription drug for safe and effective use by a veterinarian for the treatment of properly diagnosed pneumonia in sheep.

This approval does not qualify for marketing exclusivity under Section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

In accordance with 21 CFR 514.106(b)(2)(vii), this is a Category II change. This supplement provides for the use of tilmicosin in sheep, a new animal species. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

Tilmicosin is under U.S. patent number 4,820,695 expiring April 11, 2006.

6. ATTACHMENTS:

A. Facsimile R_x labeling for 50 mL, 100 mL, and 250 mL bottles.

B. Facsimile package insert